

Cabilly *et al.*  
Serial No. 10/091,430

Docket No. IVGN 382

### REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. The amendments submitted herewith are supported by the specification and original claims and do not add new matter. The amendments do not require a new search or raise new issues for consideration because they merely address issues already raised by the Examiner or define Applicants' invention more clearly. It is submitted that the amendments place the claims in condition for allowance or in better condition for appeal by reducing the number of issues for consideration on appeal. The amendments were not made earlier in the prosecution because it is maintained that the previously pending claims were allowable. Since the amendments do not add new matter or require a new search or consideration, and place the claims in condition for allowance or in better condition for appeal, entry of the amendments is respectfully requested.

### Status of Claims

Claims 73-76, 78-86, and 88-92 are pending in the application. Claims 73, 74, 78, 79, 81, 83, 84, 88, 89, and 91 have been amended. Applicants respectfully assert that the amendments to the claims add no new matter. Claims 93 and 94 are newly added.

Claims 1-72 were canceled in a previous Response to Office Action. Claims 77 and 87 are canceled herein without prejudice or disclaimer. In making this cancellation without prejudice, Applicants reserve all rights in these claims to file divisional and/or continuation patent applications.

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### Claim Amendments

Independent claims 73 and 83 have been amended to more clearly state the invention. In particular, the claim amendments to independent claims 73 and 83 clarify that it is the buffer used in the ion buffer reservoir of the apparatus that inhibits the migration of ions into the gel body, and that the buffer that inhibits ion migration comprises a Zwitter ion and an amine. The inhibition of ion migration into the gel during electrophoresis by buffers that comprise a zwitter ion and an amine is supported in the specification, including the Examples. Claim 81 and 91 have been amended to clarify that the claim refers to the migration of ions originating from the electrochemically ionizable metal. The absence of migration of ions of the electrochemically ionizable metal outside the semi-solid reservoir is also supported in the specification, including the Examples. Other claim amendments are mere wording changes for clarity or consistency, or changes in claim dependency.

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## CLAIM REJECTIONS

### 35 U.S.C. § 102 Rejections

The Office Action mailed January 25, 2005, rejects claims 73-76, 80, 82-86, 90, and 92 under 35 U.S.C. § 102(b), as being anticipated by Cabilly et al. (WO 97/41070). Applicants respectfully traverse this rejection.

Applicants have amended independent claims 73 and 83 to more clearly state the invention. As amended, independent claims 73 and 83 incorporate elements of canceled claims 77 and 87, which recited an anode buffer reservoir where the buffer comprises an amine and a zwitter ion. In contrast to the present application, Cabilly et al. do not disclose an electrophoresis apparatus that includes an anode comprising an electrochemically ionizable metal, in which the anode is located in a semi-solid ion reservoir containing a buffer having an amine component and a Zwitter ion, in which the buffer inhibits the migration of metal ions into the gel during electrophoresis, as set forth in independent claims 73 and 83 as amended.

Cabilly et al. disclose the use of a Tris-acetate EDTA (TAE) anode buffer. Neither tris-acetate nor EDTA are Zwitter ions. Thus, Cabilly et al. do not disclose a buffer having an amine component and a Zwitter ion in the anode buffer reservoir.

It is noteworthy that Cabilly et al., who do not disclose an anode buffer that includes a Zwitter ion and an amine, include an additional component, an ion exchange matrix, that is added to the anode reservoir to attempt to prevent ions originating from the anode from entering the separating gel during electrophoresis. In the present invention, a buffer that includes an amine and a Zwitter ion, as set forth in claims 73 and 83, inhibits the migration of interfering ions that originate from the ionizable metal and prevents them from penetrating into the running zone (the body of the electrophoresis gel), thereby eliminating the need for an ion exchange matrix. Since Cabilly et al. do not disclose a buffer having an amine component and a Zwitter ion in the anode buffer reservoir, Cabilly et al. do not disclose each and every element of claims 73 and 83 as amended. Therefore, claims 73 and 83 are not anticipated under 35 U.S.C. § 102(b), and Applicants respectfully assert that amended independent claims 73 and 83 are

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allowable. Claims 74-76, 80, 82, 84-86, 90, and 92 depend upon, directly or indirectly, claims 73 and 83, and therefore include all the limitations of claims 73 and 83. Therefore, Applicants respectfully assert that claims 74-76, 80, 82, 84-86, 90 and 92 are likewise allowable. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections to amended independent claims 73 and 83 and to claims 74-76, 80, 82, 84-86, 90 and 92 dependent thereupon.

### 35 U.S.C. § 103 Rejections

#### Claims 77-79 and 87-89

Claims 77, 78, 79, 87, 88, and 89 were rejected under 35 U.S.C. § 103(a) as being obvious over Cabilly et al. in view of Monthony et al (U.S 3,948,743). Applicants respectfully traverse the rejection. Claims 77 and 87 have been canceled, thus rendering the rejection moot with respect to these claims. However, it is noted that the arguments provided below are relevant to canceled claims 77 and 87, and therefore are relevant to amended independent claims 73 and 83, which include the recited elements previously provided in claims 77 and 87.

The requirements for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a) include: 1) a suggestion or motivation to combine the reference teachings be present, 2) that one of ordinary skill in the art would have a reasonable expectation of success in combining or modifying the teachings of the references, and 3) that each and every element of the claim be taught or suggested by the references (MPEP 2142). Furthermore, even where a *prima facie* case has been established, an obviousness rejection can be overcome by a showing of secondary factors such as a long-felt need, commercial success, or unexpected results (MPEP 2141).

The cited references do not render the present invention obvious because there is no suggestion or motivation to combine the references and no reasonable expectation of success. Furthermore, the unexpected results provided by the invention further establish that the present invention is not rendered obvious by the cited references.

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With regard to the lack of suggestion or motivation to combine references, it is noted that the disclosure in Cabilly *et al.*, which discloses the use of copper, lead, or silver anodes, do not teach the selection of an anode of an "electrochemically ionizable metal" for use with buffers having a zwitter ion component and an amine component, as recited in amended claims 73 and 83. There is also no teaching in Monthony *et al.*, who discloses the use of a Tris-glycine buffer, of any advantages of electrophoresis buffers containing a zwitter ion and an amine in combination with particular anode compositions. Thus the references do not, alone or in combination, provide any suggestion for one skilled in the art to combine an electrochemically ionizable metal anode with a zwitterion / amine buffer in the anode buffer reservoir in an electrophoresis system.

At the time the invention was made, there was no suggestion or motivation for combining the teachings of the cited references. Prior to the invention, the following issues that arise in the electrophoresis of biomolecules were recognized: (1) the generation of protons and hydroxyl ions at the electrodes during electrophoresis alters the pH of the running buffer, leading to nonoptimal results; (2) the use of an ionizable metal electrode prevents the formation of protons at the anode, and instead causes the formation and release of metal ions into the running buffer; and (3) the migration of metal ions into the gel interferes with electrophoresis. The invention, however, relies on the inventors obtaining the surprising result that (4) the migration of metal ions into the gel during electrophoresis can be prevented by use of particular buffers, namely, electrophoresis buffers described in the application that include a zwitter ion and an amine.

At the time the invention was made, those skilled in electrophoresis would not have been motivated to seek a solution to the problem of ion interference by combining an electrode of ionizable metal with a zwitter ion/amine buffer because a) the problem of proton formation at the anode could be solved by the use of ion exchange matrices in the electrode reservoirs, as disclosed in Cabilly *et al.*, b) the use of ionizable metal electrodes would not have appeared to be a solution, since it also led to problems of ion generation (which, however, could also be ameliorated by the inclusion of ion exchange matrices), and c) there was no expectation that a particular buffer (in the absence of an ion exchange mechanism) could prevent metal ion migration during electrophoresis. Cabilly *et al.*, for example, suggest a different strategy --the use of an ion exchange matrix--to reduce ion migration into the gel. As another method of

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eliminating interference by ion migration, Cabilly suggest the use of long gels, such that electrophoretic separation of biomolecules could occur in one area of the gel, and ion migration into the anode end of the gel would not reach the area of biomolecule separation before separation was complete (page 22, line 34 – page 23, line 8). In summary, there was no suggestion or motivation before the present application was filed, to use amine and zwitter ion buffers with electrodes that release metal ions into the electrophoresis medium. To assume that an average practitioner would have recognized that particular buffer formulations would inhibit metal ion migration from the buffer reservoir into a gel, and so be motivated to test particular buffer systems in combination with electrodes of electrochemically ionizable metals, is to use knowledge of the inventors' own discovery to point the way to the invention. This constitutes impermissible hindsight in determining the obviousness of the invention. (MPEP 2142)

For the same reasons, one skilled in the art would not have had a reasonable expectation of success in inhibiting ion migration during electrophoresis by using a zwitter ion / amine based buffer. At the time the invention was made, it was not known or expected that particular buffers might inhibit ion migration during electrophoresis. Thus one of average skill in the art would not expect to succeed in inhibiting ion migration into gels using the approach of testing different types of buffers with electrochemically ionizable metal electrodes.

Further, Applicants maintain that the unexpected result obtained by the inventors refutes the obviousness rejection. "Presence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F2d 381, 137 USPQ 43 (CCPA 1963)." MPEP (716.02). In the present invention, the novel use of a zwitterion / amine buffer in an electrophoresis apparatus that has an electrochemically ionizable metal anode led to the unexpected discovery of elimination of metal ion migration into the gel body that otherwise occurs at the anode end of the gel during electrophoresis. As detailed above, in the prior art (e.g., Cabilly et al.) an ion exchange matrix was used to overcome the problem of H<sup>+</sup> or metal ion generation at the anode and their effects during electrophoresis. The present invention eliminates the need for an ion exchange matrix in the buffer reservoir to overcome these effects. The unexpected result that the use of particular electrophoresis buffers in combination with ionizable metal electrodes inhibits metal ion migration into the separating gel allowed for the elimination of ion exchange matrices

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in the anode buffer during electrophoresis. Thus, the unexpected results of the present invention further establish that the claimed invention is not rendered obvious by the cited references.

In summary, the requirements of a *prima facie* case of obviousness under 35 U.S.C. § 103(a) were not met for claims 77, 78, 79, 87, 88, and 89 because there is no suggestion or motivation to combine the teachings of the cited references and because there is no reasonable expectation of success in combining the references. The case for obviousness under 35 U.S.C. § 103(a) is further rebutted by the unexpected result obtaining in practicing the invention. These arguments apply also to the nonobviousness of amended independent claims 73 and 83, which incorporate the elements of canceled claims 77 and 87.

#### Claims 81 and 91

Claims 81 and 91 were rejected in the Office Action as being obvious over Cabilly *et al.* Applicants respectfully traverse this rejection.

Claims 81 and 91 as amended are drawn to an apparatus and a method of making an apparatus, respectively, in which the migration of metal ions during electrophoresis does not exceed the limits of the semi-solid ion reservoir. Claims 81 and 91 depend from claims 73 and 83, respectively, and thus incorporate all the limitations of claim 73 and 83. Independent claims 73 and 83 have been amended herein to recite a buffer that comprises a zwitterion and an amine. As discussed above, Cabilly *et al.* do not disclose or suggest the use of a buffer that comprises a zwitter ion and an amine, nor identify the unexpected result that such a buffer inhibits the migration of ions of an electrochemically ionizable metal from an anode into a body of separating gel. Thus, Cabilly *et al.* do not render obvious the invention of claims 81 and 91. Applicants therefore respectfully request that the rejection be removed.

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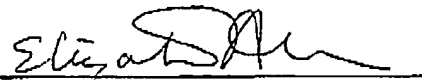
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In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Respectfully submitted,

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